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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/619,141	07/14/2003	Gabor Jarai	4-31553B	3322

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EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/619,141	JARAI ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the preliminary amendment filed on 7/14/2003. The preliminary amendment has been entered. Claims 1-17 have been cancelled. Claims 18 and 19 are currently pending and are addressed herein.

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 18 and 19 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The claims are drawn to a method for identifying a substance suitable for use in the treatment of an inflammatory disease comprising combining a candidate substance with a polypeptide (A) comprising the amino acid sequence of SEQ ID NO:2 and measuring the effect of the candidate substance on the activity of said polypeptide (A); as well as a method of identifying a substance suitable for use in the treatment of an inflammatory disease which binds to a polypeptide (A) comprising the amino acid sequence of SEQ ID NO:2 comprising mixing a candidate substance with said polypeptide (A) and determining whether binding has occurred.

Accordingly, the claims encompass SEQ ID NO:2 (the EX20 polypeptide), which Applicants assert is a G-protein coupled receptor, based on sequence similarity to a known G-protein orphan receptor.

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a

credible utility is cited in the specification for use of these receptors. Cited utilities identified by the examiner include the development of antibodies specific for EX20, and recombinant chimeric fusion proteins comprising EX20 wherein the fusion protein can be purified by conventional methods as well as method of using polypeptide in the claimed methods. These utilities are credible.

Upon identification of credible utilities, the next issue is whether there are any well-established utilities for the polypeptide. No well established utilities for this specific receptor polypeptide are identified in either the specification or in the cited prior art. Applicants assert that the instant polypeptide is a G-protein coupled receptor based on sequence homology to a known G-protein orphan receptor, GPCR HM74 (p. 18). However, the function of a polypeptide cannot be accurately determined based solely on sequence homology to another polypeptide. There is no evidence in the specification indicating any specific function of the instant polypeptide (EX20). Without a specific function, a polypeptide cannot have a well-established utility.

Given the absence of a well-established utility, the final issue is whether substantial and specific utilities are disclosed in the specification. Here, no substantial utilities which are specific to SEQ ID NO:2 are identified. As noted in the utility guidelines, methods of treating unspecified diseases, basic research on a product to identify properties, intermediate products which themselves lack substantial utility are all insubstantial utilities. No substantial utility is identified for the specific receptor polypeptide of the specification (EX20), with only speculative utilities that lack any basis provided. Further, none of the utilities asserted in the specification

are specific to the EX20 polypeptide. None rely on any unique feature of this specific polypeptide.

Furthermore, it was recognized in the art prior to the time of filing that G-protein coupled receptors (GPCRs), which includes the EX20 polypeptide (SEQ ID NO:2) as a member, constitute an enormous super-family of proteins made up of a large number of sub-families of GPCRs which can have a wide range of functions. Specifically, over 2000 different GPCRs had been identified (as evidenced by Ji et al., 1998; cited by Applicants in the 7/14/03 IDS).

Regarding the diversity of the GPCR super-family of proteins Ji teaches,

> "[GPCRs] are classified into over 100 sub-families according to the sequence homology, ligand structure, and receptor function. A substantial degree of amino acid homology is found among members of a particular sub-family... Although the majority of GPCRs mediate signal transduction via G proteins, emerging evidence indicates that some of these receptors are also capable of sending signals via alternative signal molecules, e.g. Jak2 kinases, phospholipase Cγ, or protein kinase C. These alternative pathways are an indication of the overall diversity occurring in the GPCR super-family." (See p. 17299, first column).

Therefore, it was recognized in the relevant art that time of filing that GPCRs had a wide range of functions and one of skill in the art would not be able to predict that any GPCR was involved in inflammation merely based on its classification as a GPCR.

Additionally, inflammation is a general classification for a number of specific diseases which can be caused by distinct mechanisms. For instance, chemokines are molecules which activate intracellular signaling through GPCRs and are involved in inflammation. However, different cytokines can activate distinct intracellular signaling pathways leading to vastly different effects. For instance, Kaplan (2001; cited by Applicants in the 7/14/03 IDS) teaches,

> "Chemokines are a group of cytokines that are responsible for the influx of blood cells, including T and B lymphocytes, monocytes, neutrophils, eosinophils and basophils, in allergic and other inflammatory conditions. They function as G protein-coupled

> chemotactic factors which also activate the cells with which they interact. Certain chemokines function within the afferent arm of the immune system, in which antigen is processed and antibody formation initiated, and others are active within the effector pathways of cellular immunity and late-phase allergic reactions. Th2 lymphocytes, which are critical for allergy, employ the CC chemokine receptors... Th1 reactions depend upon interferon gamma-induced CXC chemokines, which bind to [CXC-receptors]." (See abstract).

Therefore, one of skill in the art would have recognized inflammatory GPCRs as a large class of receptors which are capable of activating distinct cellular activities in response to the binding of different ligands. For instance, a CC chemokine would bind to a GPCR and activate a Th2 (lymphocyte/antibody) response, while a CXC chemokine would bind to a different type of GPCR and activate a Th1 (monocyte) response. Therefore, it would have been recognized by one of skill in the art at the time of filing that GPCRs are involved in wide range of cellular activities, including inflammation. One of skill in the art would also have recognized that GPCRs could activate distinct intracellular signal pathways which results in different inflammatory responses, depending on ligand binding.

Also, it is acknowledged that the EX20 gene is 98.8% identical to the HM74 gene, a gene that was recognized as a human GPCR. This evidence is considered sufficient for one of skill in the art to conclude that the EX20 gene encodes a GPCR. It is noted that, at the time of filing, the activity of HM74 was not known and there is no evidence that HM74 is associated with inflammation. Furthermore, shortly after the filing of the instant application, Schaub et al (2001; cited by Applicants in the 7/14/03 IDS) reported the isolation of PUMA-G, a gene which encodes a seven transmembrane protein that also has high homology to HM74 (73% identity). Schaub teaches that PUMA-G mRNA is readily induced in macrophages after stimulation with by Interferon-γ (IFN-γ), LPS, polyIC, and CpG oligonucleotides, and data indicates PUMA-G is

localized to the cell membrane (see abstract). Regarding GPCRs in general, Schaub teaches, "GPCR transduce messages of a broad spectrum of extracellular ligands such as hormones, neurotransmitters, photons, nucleotides, lipids, peptides and proteins." "One the basis of certain key sequences, they are divided into five major families: the rhodopsin-like family, the secretin-like family, the metabatrophic glutamate/pheromone family, the fungal pheromone family and the camp receptor family." (See p. 3721, second column) Schaub indicates that PUMA-G as well as HM74 and GPR31 (the two best matches with PUMA-G) have been assigned to the rhodopsin-like family, based on the seven-element fingerprint signature of this family (See p. 3721, second column). Schaub teaches several important characteristics of PUMA G, including: the sequence of PUMA-G (indicating a seven-transmembrane protein), the cellular location of PUMA-G (the cell membrane), the high amino acid identity with HM74 (a known GPCR), stimulation with IFN-γ (a pro-inflammatory cytokine), but not GM-CSF, induces PUMA-G expression in macrophages (see Fig. 6A, p. 3719). However, Schaub concludes by stating,

> "[I]mportant immunological functions can be attributed to members of the GPCR super-family. Although **no biological function can be assigned to PUMA-G, yet,** our data suggest an important role for PUMA-G in macrophage function." (Emphasis added, see p. 3722, second column).

Even with the knowledge that PUMA-G was a GPCR, its expression was induced in macrophages by stimulation with an inflammatory cytokine, and that PUMA-G had high amino acid identity to HM74, one of skill in the art could not assign a function to this GPCR without performing additional experimentation.

It is also noted that, as mentioned above, GPCRs have distinct effects on intracellular signaling mechanisms based on ligand binding. In the instant case, the specification does not disclose the ligand(s) which bind to EX20. Furthermore, although the specification indicates that

EX20 may be involved in inflammation, and mentions of several specific inflammatory diseases, the specification does not explicitly associate EX20 with any particular inflammatory disease.

Finally, with regard to the utility analysis, the current situation directly tracks Examples 4 and 12 of the utility guidelines, where a protein of entirely unknown function was characterized as lacking utility. In particular, Example 12 states that a receptor does not have utility since no "real world" use is identified, just as in the current situation. Accordingly, further experimentation is necessary to attribute a utility to the claimed protein. (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.)

Thus, the present disclosure is only a starting point for further research and investigation into potential practical uses of the EX20 polypeptide. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18 and 19 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a

well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to methods of using a polypeptide (EX20, SEQ ID NO:2) which is a receptor, and the use of the receptor to identify therapeutic compounds. Therefore, the nature of the invention is in the biological arts.

The breadth of the claims

The breadth of the claims is very broad. For instance the claims encompass using the EX20 polypeptide (SEQ ID NO: 2) to identify compounds to treat any type of inflammatory disease in any species of animal, including humans.

The unpredictability of the art and the state of the prior art

The instant polypeptide, which has been designated by the Applicants as EX20, is 98.8% identical to G-protein coupled receptor (GPCR) HM74 (Nomura et al.; 1993 cited by Applicants in the 7/14/03 IDS). However, HM74 is an orphan GPCR identified by PCR using degenerate primers. The function of HM74 and the ligand for HM74 is unknown (see Nomura et al.).

Orphan receptors are receptors for which the endogenous ligand has not been identified (see Behan et al. (WO200022129; cited by Applicants in the 7/14/03 IDS), p. 2, last paragraph). It is estimated that approximately 1,900 orphan receptors exist (see Behan, p. 2, lines 5-7). Behan teaches, "Because the endogenous ligands for orphan GPCRs are by definition not identified, the ability to discover novel and unique therapeutics to these receptors using traditional drug discovery techniques is not possible" (see p. 3, line 11-20). The specification does not identify the ligand for EX20; therefore, the specific function of the instant polypeptide is not known. Furthermore, it is not possible, using traditional techniques, to identify unique and novel therapeutics to this receptor until the receptor for EX20 is identified.

Working Examples and Guidance in the Specification

The specification discloses the sequence EX20 (SEQ ID Nos. 1 and 2). However, there is no specific disclosure of the function of the EX20 polypeptide. The specification discloses that EX20 has significant sequence similarity to GPCR HM74 (p. 18, first paragraph), and that EX20 is "preferentially overexpressed in tissues affected by various inflammatory diseases" (see p. 19, last paragraph). However, there is no specific evidence that EX20 is directly associated with any inflammatory disease. Therefore, further experimentation is required to determine the utility of the instant polypeptide.

Quantity of Experimentation

The quantity of experimentation is extremely large since the function of the instant polypeptide, has not been determined. In order to determine the function of the instant polypeptide, one would have to determine the molecules that interact with the polypeptide (such as the ligand and the intracellular signaling molecules), and determine the effects of these

interactions—such as the effects on cellular physiology, metabolism, growth, etc. It would also be advantageous to determine the effects of overexpression and depletion of the polypeptide.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Without a specific function of the instant polypeptide, one of ordinary skill would not know how to use the instant polypeptide. Furthermore, considering the breadth of the claims, the lack of guidance in the specification and the high degree of skill required, it is concluded that the amount of experimentation required to use the claimed invention is undue.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JON ANGELL
PATENT EXAMINER

JON ANGELL
PATENT EXAMINER